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COMMENTARY

The gastrointestinal tract microbiome, probiotics, and mood

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Abstract Mental health is closely linked to physical health. Depression (e.g., major depression) is highly prevalent worldwide and a major cause of disability. In a subgroup with treatment-resistant depression, standard pharmacotherapy interventions provide small if any incremental improvement in patient outcomes and may also require the application of an alternate approach. Therefore, in addition to the standard pharmacotherapies prescribed, patients will also be advised on the benefits of psychological counseling, electroconvulsive therapy, and transcranial magnetic stimulation or increasing physical activity and reducing harmful substance consumption. Numerous nutraceuticals have a beneficial role in treatment-resistant depression and include, herbal medicines of which *Hypericum perforatum* is the best studied, omega-3 fatty acid preparations, *S*-Adenosyl-L-Methionine (SAMe), various mineral formulations (e.g., magnesium) and folate (singly or in combination with B group vitamins) are prescribed to a lesser extent. Furthermore, a largely neglected area of research activity has been the role of live probiotic cultures that contribute to repairing dysbiosis (a *leaky* gut barrier abnormality) in the gastrointestinal tract (GIT). In this commentary, we build a hypothesis that in addition suggests that GIT metabolites that are elaborated by the microbiome cohort may provide novel and significant avenues for efficacious therapeutic interventions for mood disorders. We posit that the microbiome in the gastrointestinal tract is implicit as an important participant for the amelioration of adverse mood conditions via the diverse metabolic activities provided by live beneficial bacteria (probiotics) as an active adjuvant treatment. This activity is in part triggered by a controlled release of reactive oxygen species (ROS) and hence further questions the antioxidant/oxidative stress postulate.

Keywords Mood · Depression · Nutraceuticals · Gastrointestinal tract · Microbiome · Dysbiosis · Probiotics · Prebiotics

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What is already known

The gastrointestinal tract and the brain are fundamentally linked. Dysbiosis is a gastrointestinal tract barrier dysfunction due to environmental or nutritional triggers progressed by the GIT pathogenic cohort that exacerbates and maintains a *leaky gut*. Although the idea of a *leaky gut* in depression is contentious, a recent study reported that approximately 35 % of depressed individuals exhibited evidence of a *leaky gut* (Maes et al. 2013). The positive and significant associations reported, for example, were lipopolysaccharide (LPS) and oxidized LDL antibodies and IgM responses against malondialdehyde. As a cautionary note though, these were indirect measurements. Certain gut bacteria have been reported (Clarke et al. 2013) to participate in mood states. Life stressors and mood disorders

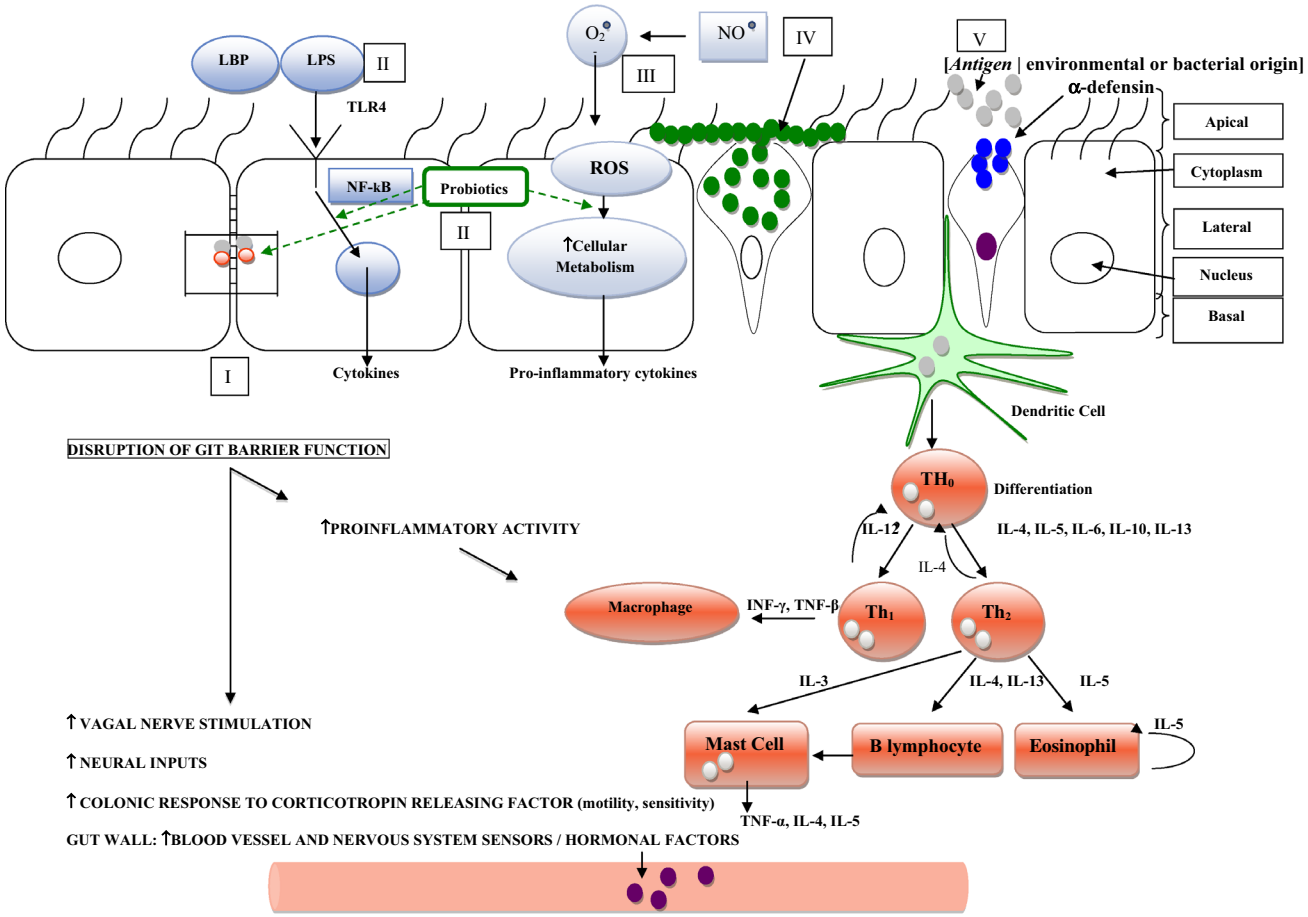

Fig. 1 A diagrammatic representation of part of the epithelial barrier of the gastrointestinal tract. *I* Tight junction and gap junction between two epithelial cells. *II* Lipopolysaccharides (LPS)/lipopolysaccharide binding protein (LBP)-mediated pathway of inflammation. *III* Reactive oxygen species (ROS)-mediated induction of cytokine production and inflammation. *IV* Mucus secreted from goblet cell forming a protective layer on the epithelial cell membrane. *V* Antigens presenting on the epithelial surface may be detected and consumed by dendritic cells and neutralized by α-defensins secreted from paneth cells. The antigen is presented to TH_0 cells followed by entry into Th_1 or Th_2 pathway depending on the antigen. Probiotics help regulate and reduce inflammation by (1) maintaining the integrity of gap junctions preventing the migration of pathogens past the epithelial barrier and (2) by preventing the activation of NF-κB caused by pathogens and compounds like LPS and ROS. This diagrammatic view also demonstrates the effects of gut dysbiosis ensuing chronic stress and depression on brain–gut axis activity. The bidirectional communication allows signals from the brain cortico-limbic structures to alter gastrointestinal function. The hypothalamus–pituitary–adrenal axis and immune system are key regulators of this axis

have long linked the brain to the gastrointestinal tract (c.f. review Vitetta et al. 2005).

What this commentary adds

The integrity of the GIT microbiome may provide a possible explanation for the differential treatment response to anti-depressive medications and be an important treatment target with multi-strain probiotic bacteria that serve to enhance different and specific functions in the gastrointestinal tract such as balancing local and extra colonic inflammatory responses linked to immune-hormonal regulation and GIT mucus production that promotes gut barrier function repair (Fig. 1). The upstream cellular signaling implicates ROS (Vitetta et al. 2013b).

Commentary

Depression is a highly prevalent mental health problem, with the burden of care second only to heart disease. At least 350 million people worldwide live with depression and it is now the leading global cause of disability irrespective of gender and age (WHO 2012).

Lifetime prevalence rates for depression in the Australian community have been estimated at 25 % for females and 12 % for males (Andrews et al. 1999). Antidepressant

medication treatment assists with acute episodes; however, its efficacy is relatively poor for chronic depressive illness, with 40 % relapsing within 15 weeks (Piccinelli and Wilkingson 1994; Katon et al. 2002; National Collaborating Centre for Mental Health (UK) 2010). Many patients experience multiple depressive episodes of increasing frequency and duration and are considered resistant to current pharmacological treatments. Studies of 15-year follow-up have found that one-fifth of depressed patients remain incapacitated or commit suicide (Kiloh et al. 1988; Lee and Murray 1988). Suicide, for which depression is the highest risk factor of morbidity, is an outcome that highlights the lack of effective treatment (Shea et al. 1987; Black et al. 1988; Brophy 1994).

The clinical response to antidepressant medication is complex. Pharmacotherapy achieves acceptable results for about 30 % of patients, mixed results for 40 % and poor results for 30 % of patients (Perovic et al. 2010). It has been reported that when (Fava 2010) the mixed medication response group is taken into account the majority of depressed patients will not experience clinical remission for their depression. Resistant depression has a complex psychiatric and physical presentation and may be better thought of as an imbalance in neurophysiology and associated comorbid physical health problems. Most antidepressants act upon monoamines (primarily norepinephrine [NE] and serotonin [5HT]) and much of the research has focused upon interactions between these neurotransmitters and their reuptake and receptor proteins. Response to antidepressant medication is slow often requiring weeks to months before any symptom response, despite immediate effects on brain monoamine transmission. The variable response to medication suggests that the monoamine augment is insufficient and other mechanisms may be involved in symptom remission (Nestler et al. 2002; Fava 2010).

More recently, there has been an acknowledgement of the importance of intracellular mechanisms involved with response to antidepressant treatments (Nestler et al. 2002; Fava 2010). Alterations of brain phospholipid composition and membrane fluidity can affect extracellular processes such as neurotransmitter–receptor binding, intracellular processes such as signal transduction and mitochondrial function, as well as eicosanoid-mediated processes, which may underlie mood disorders (Nestler et al. 2002; Fava 2010).

SAMe as a mechanistic model

One approach to directly influence neurotransmitter synthesis and receptor signaling has been methylating agents such as SAMe, which is primarily produced in the liver. SAMe is a common co-substrate involved in methyl group transfers. The methyl group (CH_3) attached to the methionine sulfur atom in SAMe is chemically reactive. This allows donation of this methyl group to an acceptor substrate in transmethylation reactions. More than 40 metabolic reactions involve the transfer of a methyl group from SAMe to various substrates, such as nucleic acids, proteins, lipids, and secondary metabolites which are all important for proper neurotransmitter function. Oral SAMe achieves peak plasma concentrations 3–5 h after ingestion of an enteric-coated tablet (400–1000 mg) with a half-life of 100 min (Najm et al. 2004; Loenen 2006). SAMe works at least as well as antidepressant medication for treatment responders and is a good candidate for co-administration as an adjuvant to SSRI medication due to its different mechanisms of action (Loenen 2006; Papakostas et al. 2010). When delivered with SSRIs in the range of 800–1600 mg per day in resistant depressive illness an increase of 36 % remission from complex resistant depression has been reported. However, 64 % of participants had a suboptimal response to the SAMe adjuvant therapy (Papakostas et al. 2010).

Of interest is that resistant depression is often accompanied by systemic inflammatory states that are reported to originate from GIT inflammation via dysbiosis (Berk et al. 2013). It is possible that at least in some cases the resulting imbalance of neurotransmitter production is a direct result of dysbiosis.

SAMe may work in additional ways including a system wide reduction of inflammatory mediators by several mechanisms including down regulating pro-inflammatory bacteria in the GIT, increasing levels of glutathione and direct or indirect signaling of growth factors (Naviaux 2014). In this way, SAMe may modestly reduce GIT inflammation and improve treatment response.

We therefore hypothesize that the gastrointestinal tract may have an important role to play in the first pass metabolism of natural compounds such as SAMe and that gut dysbiosis may limit efficacy. Given that there is a large growing awareness of the role of the gut and its microbiota influencing the gut–brain axis both in health and disease (Clarke et al. 2013) the administration of probiotics or as symbiotics (probiotics + prebiotics) as a treatment strategy to rescue gut dysbiosis may provide a biologically plausible platform for the enhanced efficacy of compounds such as SAMe. The importance exhibited by the gut–brain axis is that it provides a bidirectional flow of neuroendocrine and neuroimmunological control of organ functionality such as for the central nervous system areas and the brain, by eliciting major homeostatic control (Cryan and O'Mahony 2011; Dinan and Cryan 2013; Foster and McVey Neufeld 2013).

The gastrointestinal tract and depression

Immunomodulation in depression that is correlated to dysbiosis is a contentious issue because of the indirect measurements that have been reported (Maes et al. 2013; Berk et al. 2013; Dinan et al. 2013; Furness et al. 2013; Bravo et al. 2011). In this respect, depression was reported as accompanied by activation of immune–inflammatory pathways, and increased IgM/IgA responses to LPS of gram-negative commensal bacteria, and autoimmune reactions directed against O and NS-modified neopepitopes. This indicates that depression may be at least in part created by bacterial translocation (Maes et al. 2013). When corrected with a probiotic *Lactobacilli* in a dysbiosed rat model, GABA in the brain was increased which influenced signaling via the vagus nerve normalizing behavior and immune activity (Bravo et al. 2011). In this study, treated anxious dysbiosed mice showed lower levels of anxiety, fear, and decreased stress hormones.

While there is a lack of human studies, it is plausible that probiotics may improve symptoms of depression (Tillisch et al. 2013) through anti-inflammatory actions and an ensuring reduction in hypothalamic-pituitary-adrenal axis activity. However, these anti-inflammatory actions are unlikely to be the sole mechanism of action, GIT bacteria manufacture and secrete a range of neurochemicals. A non-exhaustive list includes certain strains of *Lactobacilli* and *Bifidobacteria* that secrete gamma-aminobutyric acid (GABA) (Dinan et al. 2013), which is an inhibitory neurotransmitter and when under expressed is implicated in anxiety and depression (Schousboe and Waagepetersen 2007). Known subspecies of *Lactobacilli* produce the essential neurotransmitter acetylcholine, which is implicated in memory, concentration, learning, and mood (Roshchina 2010). Serotonin (5-HT) is a metabolite of tryptophan and is implicated as a central mood regulating neurotransmitter (Collins and Bercik 2009). *Candida*, *Streptococcus*, *Escherichia*, and *Enterococcus* produce serotonin, while *Bacillus* and *Serratia* have the potential to produce dopamine, which is involved in a host of cognitive and mood functions (Lyte 2011).

There are only a few clinical trials that have investigated the administration of live bacterial cultures on brain functionality (Table 1). Three studies investigated mood and behavioral changes with probiotics (Benton et al. 2007; Messaoudi et al. 2011; Tillisch et al. 2013) and two other studies reported the use of probiotics in subjects diagnosed with chronic fatigue (Rao et al. 2009) and head injuries (Tan et al. 2011). The three human studies that investigated mood disturbances reported beneficial psychological effects. These studies add weight to the hypothesis that the health of the GIT microbiota is important for mental health and that there is scope for its beneficial modulation.

Table 1 Clinical studies of probiotic administration and the brain

Participant type	Study type (Number of patients)	Treatment	Duration (weeks)	Results	References
Anxiety-depressive symptoms	PCT (132)	10^8 CFU/capsule *L. casei*/65 mL/i.o.d.	3	Improvement in mood scores	Benton et al. (2007)
Chronic fatigue syndrome	PCT (39)	8×10^7 CFU/sachet *L. casei strain* Shirota/t.i.d.	8	↑ Fecal total *Bifidobacteria* and *Lactobacillus* ↓ Anxiety symptoms	Rao et al. (2009)
Healthy adults	DBPCT (25)	3×10^9CFU/sachet *L. helveticus* R0052/ 3×10^9CFU/cap *B. longum* R0175/i.o.d.	2	↓ Behaviours indicative of anxiety	Messaoudi et al. (2011)
Traumatic brain injury	SBCT (52)	0.5×10^8CFU/sachet *B. longum*/ 0.5×10^7CFU/sachet *L. bulgaricus* 0.5×10^7 CFU/cap *S. thermophiles*/t.i.d.	3	Adjustment of the Th1/Th2 imbalance ↓ Infection rate ↓ Use of antibiotics ↑ Level of IL-12	Tan et al. (2011)
Healthy women with no gastrointestinal or psychiatric symptoms	DBPCT (36)	1.2×10^9 CFU/cup *S. thermophiles* *L. bulgaricus*/b.i.d.	4	↓ Task-related response of a distributed functional network containing affective, viscerosensory, and somatosensory cortices	Tillisch et al. (2013)

Whether this probiotic triggered intonation, is transient or maintained, remains to be elucidated.

Staudacher et al. (2012) recently demonstrated an improvement in irritable bowel syndrome symptoms with a reduced FODMAP [defined as Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols] diet. The study also showed that there was a resultant reduction in concentration and proportion of luminal GIT *bifidobacteria* after 4 weeks of fermentable carbohydrate restriction. The consequences of these data may reflect a detrimental profile to the health of the GIT. Halmos et al. (2014) reported that diets differing in FODMAP content have marked effects on gut microbiota composition. Thereby positing that there may be an important negative implications with the long-term reduction of FODMAP intake, given the health benefits that these complex carbohydrates provide to the GIT microbiota and colonic health. Certainly, the specific administration of multi-strain probiotics may add important benefits in these instances by restoring the *bifidobacteria* deficit.

Other GIT scenarios with deleterious effects on the GIT microbial cohort that can elicit extreme perturbations are the administration of broad-spectrum antibiotics. One such example is rifaximin, a non-systemic orally administered antibiotic derived from rifampin and characterised by its broad-spectrum of antibacterial activity against Gram-positive and Gram-negative, aerobic as well as anaerobic bacteria (Calanni et al. 2014). It is well recognized that treatments that employ broad-spectrum antibiotics can have a detrimental impact on the commensal bacteria present in the GIT (Cotter et al. 2012) and in certain populations can lead to the development of antibiotic-associated diarrhea (Vitetta et al. 2012). The co-administration of multi-strain probiotics have been reported to reduce the prevalence of antibiotic-associated diarrhea and as such provides an opportunity to at least in part recover the unfavorable impact of antibiotics on the GIT/microbiome cohort (Hungin et al. 2013) while maintaining antibiotic therapeutic guidelines.

Discussion

We have recently reported (Vitetta et al. 2013a) (as have other groups) that ROS generated by Nox enzymes have been demonstrated to function as essential second messengers in an array of intracellular and extracellular signal transduction conduits via the rapid and transient oxidative inactivation of a distinct class of sensor proteins that incorporate in their structures, oxidant-sensitive thiol groups.

Moreover, probiotic bacteria have been reported to regulate a range of GIT physiological functions that include exerting a regulated switch control over immune responses, epithelial barrier function (loss leading to dysbiosis) and cellular proliferation (Neish 2013; Vitetta et al. 2013a). The downstream mechanism that has been advanced for the GIT control of pathogens involves a number of factors namely (1) direct anti-microbial action from the activity of bacteriocins that can inhibit pathogen gene expression; (2) stimulation of immune responses through anti-inflammatory cytokines and the rescue and further regulation of pro-inflammatory cytokines; (3) competitive marginalisation of pathogenic bacteria by competing for binding sites on the epithelial barrier and enhancing its antibacterial function; and (4) inhibition of virulence gene or protein expression in gastrointestinal pathogens. The upstream mechanism that induces this complex control of pathogenic activity implicates ROS (Amalaradjou and Bhunia 2012; Neish 2013).

Gut dysbiosis is an important causal mechanism in mood disorders and may help to explain treatment non-response. The administration of live probiotic cultures may represent an important potential adjuvant treatment strategy for diverse mood disorders. The genomic pool provided by the eukaryotic human nuclear genome in addition to the human microbiota, together harbor more than nine million specific genes that control a multitude of metabolic functions (Zoetendal et al. 2008; Yang et al. 2009).

Hence, it is plausible that such diverse and concentrated metabolic activity arising from this interaction may influence both beneficial and adverse gut barrier functionality. The GIT microbiome therefore may act as an important biosensor for the production of numerous critical metabolites influencing homeostatic control as for example the efficacy of supplements such as SAMe (or other nutraceuticals) in mood disturbances via the interaction with bacteria normally resident in the GIT.

It should be noted that probiotic bacteria encompass examples from different genera (e.g., *Bifidobacteria*, *Lactobacilli*, *Escherichia Streptococcus* or *Saccharomyces* (a yeast) recognizing that there exist a variety of different species of each genera (e.g., *Lactobacillus acidophilus*; *Lactobacillus bulgaricus*, *Lactobacillus rhamnosus*); and as such, lead to different strains within a species (e.g., *L. acidophilus La-1*, *L. acidophilus* NCFM). This taxonomic differentiation critically emphasizes that different strains from the same bacterial species may exhibit different metabolic activities and therefore may elaborate different physiological functions within the GIT (Timmerman et al. 2004), whilst expressing overlapping or specific therapeutic actions to different organ systems (Vitetta et al. 2012).

As a final thought, the RNA molecule is a prehistoric molecular entity of life on this planet. The emerging evidence proposes that there are more genes encoding

regulatory RNAs than those that encode proteins in the human genome (Morris and Mattick 2014). In bacteria, it is well known that RNA molecules serve a wide range of regulatory functions and can modulate almost every facet of cellular metabolic function (Waters and Storz 2009). RNA regulators have been reported to participate in numerous cellular physiological actions and defence mechanisms.

Research is required to better understand the mechanisms of actions in relation to mood, as well as optimal forms of probiotics/prebiotics and the delivery methods administered to ensure beneficial effects on the gastrointestinal tract. Therefore, in the near future the role of RNAs in GIT bacterial metabolic activities that control immunohormonal signals in the gut (e.g., that may affect mood states) will need to be seriously considered.

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Author contributions LV and MB conception and design of commentary. LV, MB, and HA read, amended and approved the final version of the manuscript.

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